of compounds disclosed by **Beauchamp** is sufficiently small that each member of the genus is considered anticipated; a theory of anticipation referred to by the Examiner as a *Petering*-type anticipation (though the Examiner devotes extensive discussion to the asserted anticipation also of crystalline ganciclovir monovalinate hydrochloride [GMVH], which is not an issue here).

It is settled law that, to anticipate a claim, a reference must show every element of the claim. "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987); "The identical invention must be shown in as complete detail as is contained in the ... claim." *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989), both quoted at MPEP 2131.

Applicants respectfully submit that, for the reasons discussed extensively in the Amendment under 37 CFR 1.111 mailed May 24, 1996 (received in the PTO on May 28, 1996) in App. No. 08/453,223 with regard to claims to GMVH, formulations containing it, and its use in treating herpesviral infections, a copy of which is enclosed and which is incorporated herein by reference, the compound GMVH is not anticipated by **Beauchamp**.

Applicants recognize that these arguments have been considered by the Examiner in App. No. 08/453,223 and rejected; however, these arguments constitute Applicants' position on the rejection, and so it is appropriate to respond similarly in this application.

Withdrawal of the rejection is requested.

The Rejection of Claims 23-28 under 35 USC 103(a) over Beauchamp

Claims 23-28 were rejected under 35 USC 103(a) as being unpatentable over Beauchamp, US Patent No. 5,043,339 (**Beauchamp**).

This rejection is respectfully traversed.

First, Applicants submit that GMVH is not anticipated by **Beauchamp**, as discussed above.

Second, Applicants submit that **Beauchamp** not only does not anticipate GMVH, it does not suggest it.

Applicants incorporate here by reference the arguments made above with respect to the non-anticipatory status of **Beauchamp**, as these same arguments also go directly to the non-obviousness of GMVH. When the only mono-ester [ganciclovir monoalaninate] exemplified in

Beauchamp is present as an *incidental impurity* in the corresponding bis-ester, and when the identical synthetic method applied to the valinate ester produces only the bis-valinate, Applicants respectfully submit that it is incumbent on the Examiner to do more than simply assert that GMVH is obvious because it would be desirable.

Withdrawal of the rejection is requested.

The Rejection of Claims 23-28 under 35 USC 103(a) over Verheyden et al. in view of Beauchamp et al.

Claims 23-28 were rejected under 35 USC 103(a) as being unpatentable over Verheyden et al., US Patent No. 4,355,032 (**Verheyden et al.**) in view of Beauchamp et al., *Antiviral Chemistry and Chemotherapy*, **3**(3), 157-164 (1992) (**Beauchamp et al.**)

This rejection is respectfully traversed.

Claims 23-28 were rejected as obvious over **Verheyden et al.** in view of **Beauchamp et al.**, with the Examiner reasoning that since **Verheyden et al.** shows ganciclovir, and **Beauchamp et al.** shows that acyclovir valinate is substantially more bioavailable than acyclovir, and since ganciclovir and acyclovir are similar "one skilled in the art would find it reasonable to infer information from one about the other", then it would be obvious to prepare GMV. With regard to the elements of the hydrochloride salt and crystallinity, the Examiner says, in effect, that the hydrochloride salt is suggested by **Beauchamp et al.**'s acyclovir hydrochloride, and that crystallinity is suggested by the recrystallization described in **Beauchamp et al.**'s Method A. Appellants respectfully disagree.

Verheyden et al. shows only ganciclovir and its pharmaceutically acceptable salts (of which the broad disclosure includes both acid addition salts and salts formed with bases, but the only compound exemplified is the sodium salt). There is neither disclosure nor suggestion in **Verheyden et al.** of any esters of ganciclovir. **Beauchamp et al.** shows a number of amino acid esters of acyclovir, including the L-valinate ester and its hydrochloride salt. Acyclovir valinate hydrochloride is said to be the best of these esters as prodrugs for acyclovir.

First, the Examiner reasons that it would be obvious to prepare GMV based on the attractiveness of acyclovir monovalinate. Applicants

cannot agree. While acyclovir valinate is a suitable prodrug of acyclovir, this does not lead to the conclusion that GMV is a suitable prodrug of ganciclovir. Esterification of ganciclovir, without some specific procedure involving blocking of one of the two hydroxy groups or a method of selective de-esterification, will tend to produce the bis-ester or at best a mixture of the mono- and bis-esters, which is not the GMVH of the claims. Never mind, says the Examiner, the combination of references suggests both the mono- and bis-esters, because **Beauchamp et al.** is a mono-ester, and one of ordinary skill in the art would know how to produce a mono-ester if desired. However, acyclovir valinate is a mono-ester because there is only one hydroxy group to esterify, unlike ganciclovir, which has two - the Examiner's reasoning would say that because inflating a tire on a unicycle makes it better than not inflating it, it would be obvious that one should inflate one tire on a bicycle to improve it [maybe a bicycle with one tire inflated is better than a bicycle with neither tire inflated, but one of ordinary skill would certainly prefer inflating both tires]. While the Examiner disagrees with the analogy, stating that "[T]he secondary reference establishes the desirability of the valinate prodrug," that is a simplification with which Applicants cannot agree. **Beauchamp et al.** suggests the desirability of acyclovir monovalinate, not of valinates of nucleosides. What is more, to say that one of ordinary skill in the art would know how to produce a mono-ester if one were desired does not establish that one would want to produce a mono-ester, that is, the Examiner has failed to establish within the references the motivation for the preparation of GMVH as opposed to, say, the bis-valinate. Applicants submit that a fair reading of **Verheyden et al.** in view of **Beauchamp et al.** would suggest only bis-esterification, and not the formation of GMVH; especially in view of the need for a selective process to produce the mono-ester.

Withdrawal of the rejection is requested.

The Examiner also criticizes the "Memorandum of Record" submitted in App. No. 08/453,223. Applicants enclose herewith the Declaration of Susan Malcolm, setting forth in declaration form the new data discussed in the Memorandum of Record, providing an explanation for the difference between the data in the application and in the Declaration, and establishing the relative bioavailabilities of ganciclovir and its valinate esters and acyclovir and its valinate ester. The surprising discovery that ganciclovir monovalinate is significantly more bioavailable

than ganciclovir bisvalinate and dramatically more bioavailable than ganciclovir itself (to a much greater extent than acyclovir monovalinate is more bioavailable than acyclovir) also demonstrates the unobviousness of GMVH.

The Rejection of Claims 25-26 under 35 USC 112, ¶1

Claims 25-26 were rejected under 35 USC 112, ¶1 for lack of enablement, "because the specification, while being enabling for CMV, does not reasonably provide enablement for treating herpesviruses generally."

This rejection is respectfully traversed.

The Examiner asserts that "pharmaceutical science has been unable to find a way of getting a compound to be effective for the treatment of herpesviruses generally. Under such circumstances, it is proper for the PTO to require evidence that such an unprecedented feat has actually been accomplished, *In re Ferens*, 163 USPQ 609. No such evidence has been presented."

First, Applicants respectfully submit that the Examiner has filed to make out a *prima facie* case of lack of enablement for herpesviruses other than CMV, so that no such evidence is required. The Examiner's assertions are simply that there are new herpesviruses being found, and that "[A]lthough several drugs have been developed which are effective against one or a few herpesviruses, no one has been able to get any of these drugs to work generally." Applicants submit that the Examiner's expression of doubt, without more, is insufficient to make out a *prima facie* case of lack of enablement, in the face of a general assertion of utility and enablement in the application, such as is found in the application at page 17, lines 13-27. As stated in *In re Brana*, 34 USPQ2d 1436, "only after the PTO provides *evidence* showing that one of ordinary skill in the art would reasonably doubt the asserted utility does the burden shift to the applicant . . " (emphasis added). No such evidence has been provided by the Examiner.

Second, as the Examiner acknowledges, the claimed drug (GMVH) is a prodrug of ganciclovir. As such, it will be effective at least against those disease states for which ganciclovir is effective. As stated in the present application, ganciclovir "is highly effective against viruses of the herpes

family, for example against herpes simplex and cytomegalovirus." US Patent No. 4,355,032, describing ganciclovir, states "the compound of the present invention [ganciclovir] exhibits excellent activity against Herpes Simplex virus I and II and related viruses such as cytomegalovirus, Epstein-Barr virus and varicella Zoster virus." (column 3, lines 13-17). Later in that same patent (Example 5, at column 9, line 1 - column 10, line 23) the activity of ganciclovir against herpes simplex virus 2 strain G is shown. The activity of ganciclovir against CMV is well recognized. These activities are probative of the activity of ganciclovir against herpesviruses in general, and rebut any suggestion of possible lack of enablement.

Withdrawal of the rejection is requested.

The Provisional Rejection of Claims 23-28 for Double Patenting

Claims 23-28 were provisionally rejected under 35 USC 101 "as claiming the same invention as that of Claims 51-56 of copending Application No. 08/453,223."

This rejection is respectfully traversed.

Applicants respectfully submit that the claims of the present application and the claims of App. No. 08/453,223 do not claim the same invention (i.e. are not identical). The claims of this application are directed simply to the compound GMVH, compositions containing it, and methods of treating viral infections with it. The Claims of App. No. 08/453,223 are directed to *crystalline* GMVH, compositions containing it, and methods of treating viral infections with it.

While the Examiner has asserted in App. No. 08/453,223 that there is no patentable significance in the term "crystalline", lack of patentable significance is not the test for 35 USC 101 double patenting. The test, as based on the discussion in *In re Vogel*, 164 USPQ 619, is whether a claim in one application could be literally infringed without literal infringement of the corresponding claim in the other application, and the test is a two-way test.

Although the claims of the present application are broader than those of App. No. 08/453,223 in view of their not containing the term "crystalline", it is clear that they are not identical –

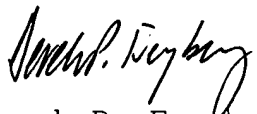
Claim 23 of the present application would be infringed by amorphous GMVH while Claim 51 of App. No. 08/453,223 would not.

Withdrawal of the rejection is requested.

Conclusion

For the reasons given above, Applicants respectfully request that the rejections be reconsidered and withdrawn, and that Claims 23-28 be allowed.

Respectfully submitted,



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